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**Potent spinal parenchymal AAVg-mediated gene delivery by subpial injection in adult rats and pigs.**

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**Authors:** Atsushi Miyanohara, Kota Kamizato, Stefan Juhas, Jana Juhasova, Michael Navarro, Silvia Marsala, Nada Lukacova, Marian Hruska-Plochan, Erik Curtis, Brandon Gabel, Joseph Ciacci, Eric T Ahrens, Brian K Kaspar, Don Cleveland, Martin Marsala

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**Public Summary:**

Effective in vivo use of adeno-associated virus (AAV)-based vectors to achieve gene-specific silencing or upregulation in the central nervous system has been limited by the inability to provide more than limited deep parenchymal expression in adult animals using delivery routes with the most clinical relevance (intravenous or intrathecal). Here, we demonstrate that the spinal pia membrane represents the primary barrier limiting effective AAVg penetration into the spinal parenchyma after intrathecal AAVg delivery. We develop a novel subpial AAVg delivery technique and AAVg-dextran formulation. We use these in adult rats and pigs to show (i) potent spinal parenchymal transgene expression in white and gray matter including neurons, glial and endothelial cells after single bolus subpial AAVg delivery; (ii) delivery to almost all apparent descending motor axons throughout the length of the spinal cord after cervical or thoracic subpial AAVg injection; (iii) potent retrograde transgene expression in brain motor centers (motor cortex and brain stem); and (iv) the relative safety of this approach by defining normal neurological function for up to 6 months after AAVg delivery. Thus, subpial delivery of AAVg enables gene-based therapies with a wide range of potential experimental and clinical utilizations in adult animals and human patients.

**Scientific Abstract:**

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